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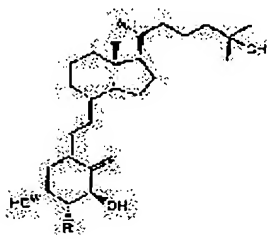

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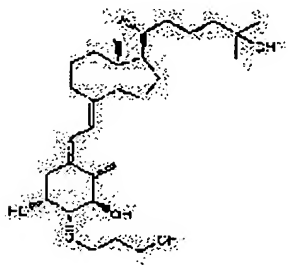

II

(57)Abstract:

PURPOSE: To obtain a synostosis promotor containing a specific active vitamin D and its derivative as active ingredients, promoting bone-repairing step after extension of bone, cut of bone, fracture, etc., and useful for shortage of treating period and prevention and treatment for re-fracture.

CONSTITUTION: This synostosis promotor contains a compound of formula I [R is H, a (substituted)lower alkyl or a (substituted)lower alkyloxy] as an active ingredient. The compound of formula I includes e.g. 2 β -(3-hydroxypropyloxy)-1- α -25-dihydroxyvitamine D3 of formula II. The agent is preferably

administered as oral agent or by systemic administration of injection, but can be locally injected into a part to be treated. The dose is preferably 0.0001-100 μ g/kg as the active ingredient.

DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to a synostosis accelerator. It is related with the drugs which prevent compaction or the refracture for a therapy period in more detail by the thing after bone extension, the bone end, fracture, and the bone grafting for which the bone repair process after bone extension or the bone end is promoted especially, and demonstrate a curative effect.

[0002]

[Description of the Prior Art] Bone extension is performed for the purpose of the amendment and correction to the patient whom the leg length difference caused the bone deformation to which the failure of the bony growth was remarkably carried out by micromelias by birth, such as a large patient and dwarfism, or accident. After bone extension gives the bone end to the bone of the side to extend, it extends to the die length which equips with a special instrument and is made into the object, conventionally various approaches were devised, and it has been applied to clinical. For example, they are the bone cutoff intramedullary nailing of a repeat, a diaphysis osteotomy or the bone end, concomitant use of the bone grafting, etc. The approach of extending gradually using the braces outside ** is common current.

[0003] When using **** braces, various designs are carried out about the class of instrument, or its technique, and an approach changes with way persons. However, after equipping with the braces outside ** fundamentally, about performing extension of a foot etc., it is common to performing the bone end and extending gradually over many hours. The most can be prevented although complication, such as a screw or bacterial infection in the steel-wire stab section, suppurative arthritis, neurovascular disorder, articular contracture, and osteoarthritis, may be seen at the time of bone extension. However, the fracture generated during the synostosis incompetence of the extension relevant to a congenital disease, rickets, etc. or a therapy period can **** complication whose prognosis is unsatisfactory. Moreover, in order to have half a year thru/or about one year from bone extension initiation to therapy termination and to have to equip with the braces outside ********, the burden to a patient is large. Therefore, it becomes the greatest good news to shorten the therapy period which includes a rehabilitation period by to promote the

synostosis or preventing the refracture.

[0004] On the other hand, with amelioration of the braces outside **, it has been improved to the approach that effectiveness is more high, and bone extension has progressed. In connection with it, using the same braces outside **, the application was devised variously and has been put in practical use in other fields. bone aiming at reconstruction of the large partial deficit produced as a result of a trauma, infection, neoplasm excision, etc. Although transport is the typical thing, it is applied also to the therapy of metaphysis section-diaphysis's osteoncus, and effectiveness is obtained. Even if it faces application [which], the same problem as bone extension arises. There is still no cure which improves these symptoms by promoting current and the synostosis. Furthermore, although it is known that a vitamin D derivative like the drugs of this invention has an operation of growth depressant action, such as calcium metabolism accommodation and a tumor cell, a differentiation-inducing operation, immunity accommodation, etc., these operations do not have the synostosis and direct relation. Moreover, the report which suggests that a vitamin D derivative is effective in the synostosis does not exist, either.

[0005]

[Problem(s) to be Solved by the Invention] This invention offers the drugs which are more effective by promoting the synostosis in the therapy process in bone extension, the bone end, etc., tends to prevent the refracture produced in a therapy period with these drugs, and tends to stabilize a prognosis.

[0006]

[Means for Solving the Problem] This invention is a general formula (I).

[Formula 2]

It is related with the synostosis accelerator which contains the compound expressed with (R shows among a formula the low-grade alkyl group which may have the hydrogen atom and the substituent, or the low-grade alkyloxy radical which may have the substituent) as an active principle.

[0007] The compound of this invention is compoundable by the approach given [for example,] in JP,61-267549,A.

[0008] In this invention, a substituent shows a hydroxyl group, a halogen atom, a cyano group, a lower alkoxy group, the amino group, the acylamino radical, etc., and is a hydroxyl group preferably.

[0009] A low-grade alkyl group shows the straight chain and the branched-chain alkyl group of carbon numbers 1-6. As an example of such a low-grade alkyl group, a methyl group, an ethyl group, n-propyl group, i-propyl group, n-butyl, i-butyl, s-butyl, t-butyl, etc. are mentioned.

[0010] A low-grade alkyloxy radical is an alkyloxy radical of carbon numbers 1-6, for example, a methoxy group, an ethoxy radical, n-propoxy group, i-propoxy group, an n-butoxy radical, an i-butoxy radical, an s-butoxy radical, a t-butoxy radical, etc. are mentioned.

[0011] As for the number of the hydroxyl groups of the low-grade alkyloxy radical permuted with the hydroxyl group, 1 is desirable, and, as for this hydroxyl group, what is permuted by the end of a chain is still more desirable. For example, 2-hydroxyethyloxy radical, a 3-hydroxy propyloxy radical, a 4-hydroxy butyloxy radical, etc. are raised, and a 3-hydroxy propyloxy radical is raised preferably.

[0012] A synostosis accelerator means the drugs which demonstrate a curative effect by preventing compaction or the refracture for a therapy period by promoting the bone repair processes after bone extension, the bone end, fracture, and the bone grafting etc. etc., and means the drugs which promote restoration of the drugs which promote the synostosis in detail, the drugs which prevent the refracture, or the bone deficit section.

[0013] After carrying out the bone end of the bone extension like the above-mentioned, a bone is gradually extended using instruments, such as braces outside **, and an opening (deficit) is formed in a bone extension. The part near the core of the opening is gradually filled up with a fibroid organization, replaces the cartilage's organization soon, is further permuted by the osseous tissue and recovers. Moreover, it is covered with growth of the osteocyte of the periosteum origin, the bone end sides extended soon construct a bridge, and the part near the outside of an opening comes to present the tubing-like bone architecture. As mentioned above, it divides roughly, a bony opening is buried according to two kinds of devices, and a bone is reconstructed. Although it is considered that the braces outside ** were removed with the event of a bone being reconstructed, and the therapy was

completed, the biggest problem is whether to have only the reinforcement to which a bone can bear a load (weight). Therefore, it is common that it is going to reconstruct the bone to which the load was applied gradually, equipped with the braces outside ** when the synostosis progressed to some extent and which had sufficient reinforcement. However, since a load is applied from the event of not securing sufficient reinforcement, the refracture may be carried out according to a fall or an unprepared load. Moreover, if it is a juvenile patient, it is common for a prognosis to be satisfactory, but old age or when a prognosis is a bad patient morbidly, and especially when, it is important to promote recovery by a certain approach.

[0014] In prevention of the refracture, if the situation which is not expected [fall] is removed, it can prevent by making dynamic reinforcement increase. The increment in dynamic reinforcement is solvable by making the dynamic reinforcement per unit bone increase by promoting the process from tissue to the hard tissue (osseous tissue), and adding minerals (many using hydroxyapatite as a principal component) to the bone formed in the deficit part.

[0015] On the other hand, it poses a problem at the time of a therapy that the therapy period continues for a long period of time. If this gives a mental or material (mainly pocketbook) pain to a patient by prognostic protraction, large sum-ization of the cost of medical treatment, etc. and not only the patient itself but a family pulls it, it leads to a national burden increasing. It is a proposition with shortening of a therapy period indispensable against relief of such disadvantageous profit. It is perfect if compaction of a recovery period, i.e., acceleration of recovery, is expectable also in solution of this problem.

[0016] The usefulness over bone extension of the active-vitamin-D derivative in this invention or acceleration of the recovery acceleration process after the bone end can be checked as follows. That is, the process of recovery after bone extension or the bone end can be visually checked by photography by the X-ray, and can be clearly distinguished about the effectiveness of drugs according to the difference of the roentgenographic finding between a medication group and the group non-prescribing a medicine for the patient. Especially the bone extension model of the rabbit later mentioned in the example can check the effectiveness of drugs on laboratory level, and moreover, since the osseous tissue of a rabbit has the same structure as Homo sapiens, it is expected that the recovery process in Homo sapiens is faithfully reproducible.

[0017] Moreover, the effectiveness of drugs over the recovery process after bone extension or the bone end can be checked by measuring the accumulation condition (bone quantity) of the hydroxyapatite to the bone formed in the deficit part with the bone quantity measuring device which used the duplex X-ray. Furthermore, the reinforcement of the bone formed in the bone deficit part or whenever [conglutination] can be numerically checked with a dynamic measuring device on the strength.

[0018] The injections which used as the principal component the solvent of a drainage system other than the oral agent manufactured by the usual pharmaceutical preparation approach of vitamin D as dosage forms of this invention are also possible. Although it is desirable as a medication method of the drugs of this invention to carry out whole body administration of an oral agent or the injections, it is also possible to carry out partial impregnation to the part for a therapy by the case. Although the dose of the vitamin D derivative of this invention changes with an adaptation disease, symptoms, etc., its 100microg is desirable from per [0.0001] kg weight.

[0019]

[Example] The example of this invention is shown below. The drugs of this invention used in the example are 2beta-(3-hydroxy propyloxy)-1alpha and 25-dihydroxy vitamin D3.

[Formula 3]

[0020] About 2cm skin incision was added to Japanese white **** of about ten weeks of after the birth under the Nembutal anesthesia at the leg bone inside. After adding the same incision also as the periosteum, the periosteum was carefully exfoliated over the perimeter. The bone end was carried out after [inside / leg bone diaphysis] stabbing four screws using the GIGURI saw between the screws of 2 Motome and 3 Motome, it equipped with the braces outside ** (Orthofix M-100), and the incision section was closed. Bone extension (10mm) for ten days was performed at the 1mm [/day] extension rate after the waiting period for ten days. Administration of the drugs of this invention was performed from the day which started bone extension, and was administered hypodermically twice per week by the dose 0.05 and 0.01microg/kg. Bone quantity was measured weekly using the duplex X-ray bone quantity measuring device after medication.

[0021] A change of the bone quantity which can be set at least to the extension from the bone extension termination back at drawing 1 with time was shown. The bone quantity of the control group which prescribed only the solvent for the patient increased after extended termination till the 3rd week, and the pattern which decrease in number gradually after that was obtained. the medication of this invention -- the bone quantity like a bone extension -- contrast -- comparing -- significant -- increasing -- the effectiveness -- a dosage -- it was

anaclitic. Moreover, by 0.05microg/kg administration group of the drugs of this invention, the peak of the increment in bone quantity came to be accepted at the 2nd week, and it became clear that the increment in bone quantity appeared at an early stage more rather than a control group.

[0022] Since it is generally known that bony reinforcement shows the increment in bone quantity and forward correlation, it is shown that this result made the dynamic reinforcement like a bone extension increase by having prescribed the drugs of this invention for the patient. Moreover, since the peak of the increment in bone quantity appears at an early stage by administration of the drugs of this invention, it is shown clearly that the recovery process after bone extension is promoted by the drugs of this invention.

[0023] The X-ray image of 0.05microg/kg administration animal of the contrast for the 3rd week at the event and the drugs of this invention was shown in drawing 2 after bone extension termination. Although thin shading was only observed at least to the bone extension in the control group, for the medication animal of this invention, this shading was deep and, also visually, it has checked that the increment in bone quantity, i.e., recovery, is notably promoted by the medication of this invention.

[0024] Several months are usually taken to shift to the so-called rehabilitation to which it begins to apply a load gradually through a patient's rest period after extended termination from several weeks. That shift stage is determined from a roentgenography image opinion, and if this visual decision stage can be discerned more early, it will lead to compaction of a therapy period.

[0025] The drugs of this invention promoted the recovery process of the bone extension (bone deficit part) in a rabbit bone extension model, and it became clear from the above result that they are the drugs which enable compaction of a therapy period by making bony dynamic reinforcement increase at an early stage. This effectiveness is useful to not only bone extension but fracture, restoration of a bone deficit part, or conglutination of the bone after osteotomy enforcement.

[0026]

[Effect of the Invention] The drugs which contain the active vitamin D of this invention and its derivative as an active principle are dramatically useful for the therapy of the disease accompanied by destruction of osseous tissues, such as bone extension, the bone end or fracture, and a bone deficit, or the more positive therapy of recurrence prevention etc.

2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] General formula (I)
[Formula 1]

It is the synostosis accelerator which contains the compound expressed with (R shows among a formula the low-grade alkyl group which may have the hydrogen atom and the substituent, or the low-grade alkyloxy radical which may have the substituent) as an active principle.
[Claim 2] The synostosis accelerator according to claim 1 characterized by being the low-grade alkyloxy radical by which R is permuted with the hydrogen atom or the hydroxyl group.
[Claim 3] The synostosis accelerator according to claim 1 characterized by being the low-grade alkyloxy radical by which R is permuted with the hydroxyl group.
[Claim 4] The synostosis accelerator according to claim 1 characterized by R being a 3-hydroxy propyloxy radical.
[Claim 5] The synostosis accelerator according to claim 1 characterized by promoting the synostosis in bone extension.
[Claim 6] The synostosis accelerator according to claim 1 characterized by promoting the synostosis after an osteotomy.
[Claim 7] The synostosis accelerator according to claim 1 characterized by promoting the synostosis after fracture.
[Claim 8] The synostosis accelerator according to claim 1 characterized by promoting the synostosis after the bone grafting.